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Development of an Enantioselective Amine-Silver Co-Catalyzed Conia-Ene Reaction

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The development of a novel cooperative catalytic system for an amine-silver co-catalyzed Conia-ene reaction of alkyne-tethered C-H-acidic compounds is reported. By using a cost-effective silver salt and a small diamine for the *5-exo-dig*-cyclization the cyclopentane products are obtained in very good yields. The enantioselectivity of the reaction could be controlled by exchanging the diamine co-catalyst with a cinchona-derived primary amine.

Since its development by Conia and Le Perchec in 1973, the Conia-ene reaction, a variation of the classic ene-reaction, has attracted much interest and was not only further developed, but also employed in the synthesis of complex molecules.^{1,2} In the beginning strong acids and bases were used to promote the cyclization reaction, but were soon replaced by metal-based Lewis acids activating the nucleophile, the alkyne, or both.

Especially pure alkyne activation is very common, because it allows for remarkably mild reaction conditions. The first Conia-ene reaction relying on this activation mode was described by Toste and co-workers in 2004, who used PPh₃AuCl and AgOTf to *in situ* generate the active [PPh₃Au]OTf catalyst.³ The development of the improved catalyst [PPh₃Au]NTf₂ by Gagosz et al.⁴ and sterically less hindered phosphine ligands for larger ring synthesis by Sawamura et al.⁵ further promoted this field.

Despite the large number of non-enantioselective protocols using a broad range of metals, including not only gold, but for example also $In,^6$ Zn,⁷ or Co⁸, asymmetric methods remain scarce and usually rely on the cooperative activation with a complex heterobimetallic catalyst system and a chiral ligand (Figure 1, a). Toste et al. were the first to report an asymmetric version using a Pd(DTBMSegPhos) complex and Yb(OTf)₃ as co-catalyst.⁹ Later catalyst systems consisting of La(OiPr)₃/AgOAc¹⁰ or Zn(OAc)₂/Yb(OTf)₃¹¹ in combination with



Fig. 1 Comparison of known approaches and our work for an enantioselective Conia-ene reactions. (L = ligand, M_h = hard metal, M_s = soft metal)

chiral additives were employed. Following a different approach, carrying out Conia-ene reactions in the presence of a copper catalyst and a chiral urea¹² or an iron-salene complex¹³, Dixon et al. and White et al. obtained excellent results (Figure 1, b).Combining both general approaches, we envisioned that the cooperative combination of a primary amine for the enamine activation of the ketone and especially cost-efficient silver catalysts for the electrophilic activation of the alkyne would provide the ideal properties for the Coniaene reaction of alkyne-tethered β-ketoesters and related compounds without the need of a second metal co-catalyst (Figure 1, c). Furthermore, readily available, chiral amines could be used to easily control the stereoselectivity of the cyclization process. To the best of our knowledge there is no precedence in the literature of a silver-catalyzed addition of an enamine to an alkyne.

The initial study towards the Conia-ene reaction of β ketoester **1a** showed that no cyclization occurred in the presence of *tert*-butylamine when silver carbonate and TFA were used as co-catalysts. Interestingly, the reaction proceeded smoothly when the bifunctional primary amine **A** was used instead. Possibly the second amine group allows for an interaction with the silver; thus, fixing the substrate in a reactive conformation. In the screening of several silver sources (Table 1, entries 1-3)¹⁴ soluble and insoluble species proved to be effective and AgNTf₂·MeCN was identified as the best silver source. Especially the use of CHCl₃ as solvent had a further beneficial effect on the outcome of the cyclization

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Entry	[Ag] ^b	A [mol%]	Acid (mol%)	Solvent	Yield ^c [%]
1	Ag ₂ O	20	TFA (20)	CH_2Cl_2	81
2	AgSbF ₆	20	TFA (20)	CH_2CI_2	80
3	$AgNTf_2$	20	TFA (20)	CH_2CI_2	84
4	$AgNTf_2$	20	TFA (20)	CHCl₃	84
5	$AgNTf_2$	20	TFA (20)	CCI ₄	74
6	$AgNTf_2$	20	TFA (20)	1,2-DCE	78
7	$AgNTf_2$	20	TFA (20)	toluene	78
8	$AgNTf_2$	20	B (20)	CHCl₃	86
9	$AgNTf_2$	20	C (20)	CHCl₃	86
10	$AgNTf_2$	20	D (20)	CHCl₃	86
11	$AgNTf_2$	10	B (10)	CHCl₃	89

^a The reactions were carried out with β-ketoester 1a (0.25 mmol), [Ag] (10 mol%), amine A, and acid in 0.25 mL of the given solvent (c = 1 M) at ambient temperature. ^b In the case of AgNTf₂, the acetonitrile complex AgNTf₂·MeCN was used as the silver source. ^c Yield of the isolated product 2a.

reaction leading to the cyclopentane 2a in 84% yield (entry 4). Using different acid co-catalysts marginally effected the reaction efficiency and similar yields were obtained for all tested acids (entries 8-10). Finally, the catalyst loading of the amine A and acid B could be decreased to 10 mol%, respectively, even giving a slightly increased yield of 89% (entry 11). Further decreasing the catalyst loading of the amine, the acid, and the silver salt negatively influenced the catalytic activity.

Encouraged by the results of the non-asymmetric version of the amine-silver co-catalyzed Conia-ene reaction, we set our focus on the enantioselective variation of the protocol. We envisaged that the use of a chiral amine should provide the necessary face discrimination in the transition state of the Conia-ene reaction. Our first choice were cinchona-derived amines naturally incorporating the primary-tertiary amine motif in a chiral environment. Using quinidine amine E we started the investigation towards an asymmetric Conia-ene reaction by screening various metal species as carbophilic Lewis acids (Table 2).14 The use of [Ph₃PAu]NTf₂ catalyst introduced by Gagosz and co-workers⁴ and In(OTf)₃ as part of the catalyst system lead to the cyclized product; albeit no enantioselectivity was observed (entries 1, 2). Only silver salts could convert the β -ketoester **1a** in good yields in an enantioselective fashion. Insoluble silver sources, e.g. Ag₂CO₃, usually gave slightly higher yields; whereas the reaction with silver salts containing weakly coordinating counterions, e.g. AgSbF₆, proceeded with higher stereocontrol (entries 3-9). With 63% yield and 75% ee AgNTf₂·MeCN was identified as the most effective silver salt.

For the next set of variations, we first screened various diamine and acid co-catalysts (Scheme 1) and found that

Table 2 Screening of different metal sources for an enantioselective Conia ene reaction

Me Me	20 mol% quinidine E 20 mol% TFA 10 mol% [M] CH ₂ Cl ₂ , rt	Me OE	t OMe	
Entry	[M]	<i>t</i> [h]	Yield ^b [%]	ee ^c [%]
1	[PPh ₃ Au]NTf ₂	24	94	0
2	In(OTf)₃	48	78	1
3	AgNTf ₂ ·MeCN	20	63	75
4	AgOTf	44	45	72
5	AgSbF ₆	42	35	74
6	AgBF ₄	42	38	74
7	AgF	65	45	67
8	Ag ₂ SO ₄	72	24	62
9	Ag ₂ CO ₃	48	84	43

^{*a*} The reactions were carried out with β -ketoester **1a** (0.25 mmol), [M] (10 mol%), 9-epi-quinidine amine E (20 mol%), and TFA (20 mol%) in 0.25 mL CH₂Cl₂ (c = 1 M) at ambient temperature. ^b Yield of the isolated product 2a. ^c Determined by HPLC with a chiral stationary phase.

quinine- and cinchonidine-based catalysts gave good yields, but lower ee values. Hydrogenation of the vinyl group at the quinuclidine ring can strongly influence the catalyst folding and thus effect the selectivity. Indeed, we observed an increased enantioselectivity of 78% ee and a comparable yield of 61% when using the hydrogenated quinidine amine J. Furthermore, only low reaction efficiency or enantioselectivity was achieved when bifunctional amines with a secondary amine or thiourea moiety were employed. Subsequently, amine J was used to investigate the effect of different acidic co-catalysts.



Scheme 1 Screening of various chiral amines and acidic additives for an enantioselective Conia-ene reaction. The first set of reactions was carried out with β -ketoester **1a** (0.25 mmol), AgNTf₂·MeCN (10 mol%), amine, and TFA (20 mol%) in 0.25 mL CH_2Cl_2 (c = 1 M) at ambient temperature. The screening of the acids was analogous carried out with amine J.

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Table 3 Optimization of the enantioselective Conia-ene reaction ^a					
Me Me	o OEt	20 mol% J 20 mol% TFA [Ag] N solvent, 7	de to the total of total of the total of	Et OMe	
Entry	Solvent	[Ag] [mol%]	<i>T</i> [°C]	Yield ^b [%]	ee ^c [%]
1	CHCl₃	10	rt	69	48
2	CCl ₄	10	rt	35	69
3	1,2-DCE	10	rt	45	60
4	EtOAc	10	rt	57	80
5	DMF	10	rt	63	86
6	toluene	10	rt	14	80
7	MeOH	10	rt	76	90
8	MeOH	10	40	85	90
9	MeOH	10	0	82	91
10	MeOH	10	-20	28	89
11	MeOH	2.5	0	86	95

^a The reactions were carried out with β-ketoester 1a (0.25 mmol), AgNTf₂·MeCN (10 mol%), 9-epi-quinidine amine E (20 mol%), and TFA (20 mol%) in 0.25 mL CH₂Cl₂ (c = 1 M) at ambient temperature. ^b Yield of the isolated product 2a. ^c Determined by HPLC with a chiral stationary phase.

Independent from the acidity the use of N-Boc-protected amino acids and pTSA resulted in lower enantioselectivities and TFA was used for the further optimization of the reaction conditions (Table 3).¹⁴ The nature of the solvent tremendously influenced the efficiency of the reaction with respect to yield as well as stereoselectivity. Usually more polar solvents were better suitable for the cyclization reaction leading to the cyclopen-tanes with up to 86% ee (entry 5). To our surprise, as protic solvent further increased the methanol enantioselectivity to 90% and the yield to 76% (entry 7). We then continued to vary the temperature, which only had a small effect on the selectivity; albeit decreased yields were observed for the reaction at -20 °C (entries 8-10). Finally, the loading of the silver source could be reduced to 2.5 mol%, which increased the yield to 86% and the enantioselectivity to 95% ee (entry 11).

With the optimized reaction conditions at hand we set out to extend the scope of the novel cooperative amine-silver cocatalyzed Conia-ene reaction (Table 4). A series of β-ketoesters 1 could be converted into the corresponding cyclopentanes 2 with high yields of up to 97% and high enantioselectivity of up to 95% (entries a-g). In contrast to the bulkiness of the ester group, the steric hindrance of the keto group prevented an efficient reaction and higher temperatures had to be employed (entries h-l); unfortunately, lower enantioselectivities resulted in these cases. In addition, β -diketones and β ketosulfones were also suitable substrates for the amine-silver co-catalyzed Conia-ene reaction (entries m-p). Depending on the steric hindrance of the substrates elevated temperatures were also necessary. The cyclic diketones and sulfones were obtained in moderate to good yields and up to a moderate level of enantioselectivity.¹⁵ Substrates with a tBu-keto group, an alkyne-tethered β -ketoamide, and internal alkynes were no suitable substrates for this catalyst system.¹⁶

		1	2.5 mol% AgNTf ₂ ·MeCN	2	
	-1	- 2	"Racemic" Method ^a	Asymmetric N	lethod ^b
2	R⁺	R ²	Yield ^c [%]	Yield ^c [%]	ee ^d [%]
а	Me	COOEt	89	89	95
b	Me	COOMe	77	97	93
с	Me	COOBu	86	91	93
d	Me	COOallyl	77	94	87
е	Me	COO <i>i</i> Pr	75	92	93
f	Me	COO <i>t</i> Bu	89	97	91
g	Me	COOBn	97	93	88
h	Et	COOMe	95 ^e	93 ^e	11
i	Et	COOEt	78	97 ^e	27
j	Pr	COOEt	46 ^e	32 ^e	51
k	<i>i</i> Pr	COOEt	54 ^f	20 ^{<i>g</i>}	0
I	Ph	COOEt	54 ^f	55 ^e	65
m	Me	COMe	67	-	-
n	Me	COPh	90 ^e	86 ^e	70
ο	Me	SO ₂ Me	93 ^f	-	-
р	Me	SO_2Ph	39 ^f	46 ^{<i>g</i>}	11

^{*a*} The reactions were carried out with β -ketoester **1** (0.25 mmol), AgNTf₂·MeCN (10 mol%), A (20 mol%), B (20 mol%) in 0.25 mL CHCl₃ (c = 1 M) at ambient temperature. ^b The reactions were carried out with β -ketoester 1 (0.25 mmol), AgNTf₂·MeCN (2.5 mol%), dihydro-9-epi-quinidine amine J (20 mol%), and TFA (20 mol%) in 0.25 mL MeOH (c = 1 M) at 0 °C. ^c Yield of the isolated product 2. ^d Determined by HPLC with a chiral stationary phase. Synthesized at 40 °C. ^f Synthesized in toluene at 80 °C. ^g Synthesized at 60 °C.

Thereafter, we demonstrated the synthetic utility by converting the β -ketoester **1a** on a gram-scale to cyclopentane 2a with the same level of yield and stereoselectivity (Scheme 2). Additionally, the germinal diacylated exo-methylene cyclopentane 2a could be transformed to the corresponding epoxide 3, as well as the alcohols 4 and 5 in high yields by standard procedures.

We propose that the first step of the mechanism is the



Scheme 2 Gram-scale transformation of β -ketoester 1a and subsequent epoxidation as well as reduction of cyclopentane 2a.

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Table 4 Substrate scope of the novel amine-silver co-catalyzed Conia-ene-reaction 07J

10 mol% A 10 mol% B 10 mol% AgNTf₂·MeCN or 20 mol% J

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condensation of the primary amine with the keto group in the presence of the acidic co-catalyst leading to enamine 6 (Scheme 3). The failure of the reaction in the case of internal alkynes suggests the formation of the silver acetylide 9 that results after the coordination of a silver cation to the alkyne (7) and the loss of a proton from intermediate 8. The subsequent attack of the enamine nucleophile to the acetylide is energetically unfavourable, because the intermediate anion 10 lacks electronic stabilization; however, protonation, protodeargentation, and hydrolysis of the iminium ion 12 leads to the cyclopentane 2. A second pathway is possible when the silver acetylide 9 is activated by the coordination of a second silver cation. In this case the 5-exo-dig-cyclization leads to the potentially more stabilized disilver species 14 that after double protodeargentation and imine hydrolysis yields the cyclic product 2. To gain deeper insight in the mechanism we conducted a deuterium-labelling experiment with a substrate bearing deuterium on the alkyne; interestingly, no deuterium was incorporated in the product suggesting the formation of an acetylide intermediate (e.g. 9).17 However, when the reaction was carried out in deuterated methanol mainly a cyclopentane was formed that contained deuterium at both olefinic positions. Unfortunately, with that result we were not able to conclude, whether the reaction proceeds in a cis- or trans-fashion and which pathway is preferred.

In conclusion, we have developed a novel cooperative catalytic system consisting of a silver salt and a diamine for the amine-silver co-catalyzed Conia-ene reaction of alkynetethered β -ketoesters, β -diketones, and β -ketosulfones. The enantioselectivity of the cyclization reaction could easily be controlled by replacing the diamine with a cinchona-derived



 $\ensuremath{\textbf{Scheme 3}}$ Proposed mechanism of the novel a mine-silver co-catalyzed Conia-ene reaction.

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- 16 A complete list of unsuitable substrates can be found in the ESI.
- 17 The results of the deuterium-labelling experiments and a model for the enantioselectivity are provided in the ESI.

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